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CONTRACT NO: DAMD17-90-C-0024

TITLE: DEVELOPMENT OF A MOLDABLE, RESORBABLE APPLIANCE FOR USE IN MAXILLOFACIAL SURGERY

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REPORT DATE: June 27, 1991

TYPE OF REPORT: Final Report

PREPARED FOR: U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for public release;
distribution unlimited

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	27 June 1991	Final Report (3/15/90 - 3/14/91)

4. TITLE AND SUBTITLE
Development of a Moldable, Resorbable appliance for use in Maxillofacial surgery

5. FUNDING NUMBERS
Contract No.
DAMD17-90-C-0024
61102A
3M161102BS16.EE.032
WUDA346174

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8. PERFORMING ORGANIZATION REPORT NUMBER
SRI-APC-91-571

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Development Command
Fort Detrick, Frederick, Maryland 21702-5012

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

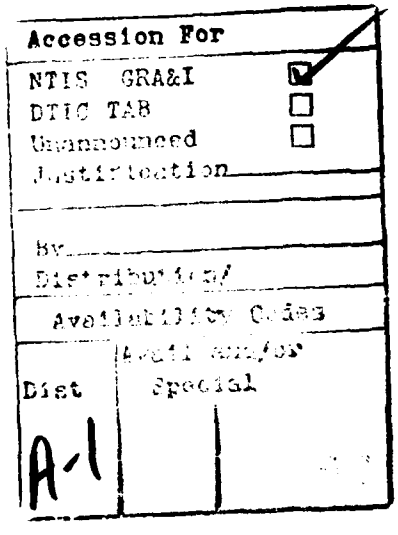
Survivable, maxillofacial injuries, such as those arising from military conflicts, often require open or closed reductions that involve the use of metallic plates, screws, and wires. Because these are nonresorbable, internal-fracture-fixation plates made from poly(DL-lactide) and reinforced with calcium metaphosphate (CMP) fibers have been designed to provide initial rigidity and weaken gradually. This exercises the newly formed bone, thereby strengthening it. Also, the need for a second surgery is obviated. Because the biodegradable, composite plates are not readily conformable to closely match the contour of bone and must be cut, drilled, and beveled to the required size and shape, alternative approaches to fracture fixation are desirable. This investigation delved into the feasibility of preparing moldable, moisture-curable poly(DL-lactide)s as matrix for CMP whiskers. Various synthetic schemes were investigated to put isocyanate functionality onto alcohol-terminated prepolymers. At the time of surgery, the curable polymer may be cured by moisture or other curing agents as it is mixed with CMP whiskers. In curing with moisture, foaming can be expected to induce a

14. SUBJECT TERMS	15. NUMBER OF PAGES
Biodegradable Polymers; Polylactic acid; Bone Splint; Calcium Metaphosphate; Biodegradable Fibers; RA II	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

13. Abstract (continued)

porosity in the implant. It is concluded from this study that appropriate, biocompatible-curing agents to be used with alcohol-terminated prepolymers represent a preferred route to resorbable, fracture-fixation materials that can be quickly and simply shaped at the time of surgery.



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22 JUNE 91

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TABLE OF CONTENTS

		Page
I.	INTRODUCTION	1
II.	EXPERIMENTAL METHODS	4
	A. Materials	4
	B. Synthesis of Diol- and Triol-Terminated Prepolymers	5
	C. Modification of Alcohol-Terminated Prepolymers by the Succinic Anhydride Route	5
	D. Model Studies on the Modification of the Diol Prepolymer	7
	E. Modification of Ethylene Glycol by the α-Haloacetyl Halide Route	8
	F. Modification of Diol Compounds by the Diacid Chloride Route	10
III.	CONCLUSIONS AND RECOMMENDATIONS	12
IV.	REFERENCES	14
V.	APPENDIX (Figures 1 through 14)	

DEVELOPMENT OF A MOLDABLE, RESORBABLE APPLIANCE FOR USE IN MAXILLOFACIAL SURGERY

I. INTRODUCTION

The search for an ideal, internal-fracture fixation has led to the attempted development of a moldable, resorbable material that can be cured in situ on demand. Once in place, the implant will provide enough initial rigidity to allow primary osseous union and callus formation followed by a gradual reduction in stiffness, commensurate with the healing bone's ability to serve in a load-bearing capacity. In the past, clinical success in the internal fixation and stabilization of mandibular fractures was achieved through the use of metallic plates. However, metallic plates offer an advantage only during the early stages of healing for achieving primary osseous union. Thenceforth, the metallic plates become a detriment to the continued restoration of bone strength. Today an evolution from metallic plates is occurring because of several problems associated with its rigidity and permanence.

In the restoration of broken mandibles, rigid, fracture-fixation plates have led to an extremely slow restoration of the strength of the mandible to its original level when compared to callus formation (McKibbin, 1978). In addition, because the generation of external callus is inhibited by the absence of mechanical stimulation at the fracture site, radiological assessment of the extent of healing by primary osseous union is difficult.

The permanence of the fixation plates also affects the way the mandible actively remodels itself to efficiently bear the work-load. If a rigid metallic plate is not removed when the fracture has healed, it continues to carry a majority of the load over its span. Forces that would normally be directed through the bone at the fracture site are transmitted around the fracture instead. As a consequence, osteoporosis and atrophy occur (Stromberg and Dalen, 1976; Uthoff and Dubuc, 1971). The result is an increase in bone formation at the site of stress transfer at the ends of the plate, a shift in the neutral axis of the bone/plate construct, and net-bone loss in the stress-shielded regions (Slatis et al., 1980; Szivek et al., 1981). If removal of the plate becomes necessary at a later date, the remaining bone may not be sufficiently strong to support normal loads and may refracture unless the mandible is protected by reduced load-bearing.

As it became apparent to researchers that rigidity and permanence could be problematic in internal-fracture-fixation systems, it also became apparent that the major difficulty in determining the optimum mechanical properties of a mandibular-fixation appliance involved the conflicting requirements that existed during the two phases of healing (Bradley et al., 1979). Initially, the plate must have sufficient stiffness to allow bony union with little bending. However, some degree of mechanical deformation at the fracture site is desirable to promote the formation of external callus. This will rapidly achieve bony union and subsequently restore the strength of the fractured bone to its original level. Furthermore, a less precise anatomical reconstruction is required with the generation of callus (Taylor et al., 1982; Uhthoff and Finnegan, 1983).

There have been attempts to alleviate problems associated with stress shielding. Extensive efforts have centered on the use of less-rigid materials for internal-plate fixation to allow for more implant deformation for a given load, and therefore raise the load-level in the bone. Examples of alternative materials are more flexible metals (Nunamaker and Perren, 1980), polymeric-backed metal plates (Badgy et at., 1985; Daniels et at., 1985), fiber-reinforced composites (Woo et al., 1980; Gillett et al., 1985), and thermoplastics (Brown and Vandergrift, 1981; Tonino and Klopper, 1980). There have also been studies that compared plates of various stiffness in an effort to define the optimum mechanical properties for bone plates (Carter et al., 1981; Taylor and Bradley, 1983). Although differences in the experimental methods of these investigations make it difficult to precisely define these properties, the results indicate that more compliant plates promote callus formation and induce less stress-protection effects than metallic plates. They also show that the continuous attachment of a bone plate, regardless of its compliance, results in a loss of bone mass and delayed remodeling.

Regardless, these efforts did not simultaneously address the problems associated with both the rigidity and permanence of the devices. Thus, it is now postulated that the ideal mandibular-fixation appliance should possess enough initial rigidity of the device to allow primary union and callus formation, followed by a gradual reduction in stiffness commensurate with the healing bone's ability to serve in a load-bearing capacity. One way of achieving this goal, without the need for additional surgical intervention, would be to use a material that biodegrades into by-products that are neither toxic nor harmful to the patient. While there are several biodegradable polymers available with strengths commensurate to that of virgin bone, their moduli are low and cannot, by themselves, provide enough rigidity and at the same time satisfy limited-size restraints (Tunc, 1985). The technique of reinforcing these polymers with fibers of the same or different biodegradable polymers has been used at SRI (Dunn et al., 1979) and other laboratories (Vert and Garreau, 1985) but does not increase the strength to the point where the material is viable for demanding mandibular-fixation applications.

Nonresorbable, reinforcing fibers have also been used successfully to increase the strength and rigidity of biodegradable polymers for internal fracture fixation or stabilization (St. John, 1983; Casper et al., 1981; Parsons et al., 1983). Carbon fibers are the most commonly used reinforcing medium. The polymer matrix biodegrades while the reinforcing fibers disintegrate in the body and thereby gradually transfer the load from the appliance to the healing bone. These studies have demonstrated the principle that fiber reinforcement can strengthen biodegradable polymers to the point where they are useful for mandibular fixation. However, because the reinforcing fibers were not affected by body fluids, these studies did not address the problems that might result when the reinforcing fibers also are bioresorbable. Moreover, these composites are not truly biodegradable because the reinforcing component stays behind after the absorbable matrix is gone.

Eventually, nonpolymeric, degradable materials were developed as reinforcement, which led to a totally resorbable composite (Dunn and Casper, 1987). Totally resorbable composites have been prepared previously using both poly(L-lactide) (L-PLA) and poly(DL-lactide) (DL-PLA) as the matrix polymers and calcium metaphosphate (CMP) glass fibers as the absorbable high-modulus

reinforcement. The fabrication of the totally resorbable composites was accomplished by a tedious process using precision molds and by adopting a solvent-heat-pressure technique whereby individual layers of polymer film and CMP fibers were pressed into the final composite. Although these first composites were crude in construction, they had flexural strengths and moduli similar to that of virgin bone. It was this type of composite that was used by USAIDR to repair mandibular fractures in canines in 1986.

At that point, SRI had evaluated only whole composites before and after incubation in saline. The results were encouraging because initial strengths were in excess of targeted values, and gradual strength loss in saline was not excessive. However, the plates that were implanted into the dogs were cut, beveled, and drilled with holes to accommodate the bone screws. This treatment of the plates apparently exposed CMP fiber ends, which readily wicked fluids into the composite. This fluid had a catastrophic effect on the polymer/fiber interface and resulted in composites that quickly lost a majority of their strength. These findings were previously confirmed in the SRI laboratory where it was found that severely cut plates could loose 90% of their strength after just one day in saline, while it took plates that were not cut about eight weeks to weaken to this level. The polymer/fiber-interface problem was pinpointed through a series of tests using either resorbable or nonresorbable, reinforcing fibers in either biodegradable- or nonbiodegradable-polymer matrices. Polypropylene, epoxy, DL-PLA, and polycaprolactone plates were reinforced with either CMP or normal, nonresorbable fiberglass. The time/strength profile of these plates after incubation in saline showed that the totally resorbable composites weakened much faster than all of the other plates.

Efforts were then turned toward the preservation of the polymer/fiber interface under an aqueous environment. Alternative, resorbable, reinforcing fibers, the percent of CMP fiber loading, different biodegradable, polymeric matrices, fiber sizings and coatings, and tedious fabrication techniques were previously investigated in an effort to yield a more durable, resorbable composite. What resulted in the best combination was a high-molecular-weight (MW) L-PLA composite reinforced with 35% CMP fibers and continuously coated with polycaprolactone (PCL). The construction technique involved solvent, heat, and pressure to compress very thin laminates of L-PLA powder and films and CMP fibers. The PCL outer coating is applied from a fluidized bed after the plates are cut to size and drilled. Plates of this type were provided to USAIDR in a previous contract for evaluation in the repair of mandibular fractures in dogs.

Although SRI developed a totally resorbable-fixation appliance for use in maxillofacial surgery, it still has shortcomings that must be overcome before it can be conveniently used in a clinical setting, particularly those in mass-casualty situations that arise as a direct result of military conflicts. First, because the polymer-matrix material is a thermoplastic, it cannot be configured at the time of surgery to match the contour of the patient's mandible. If drastic cutting, grinding, and scraping is used to modify the shape of the plate, catastrophic results can be expected. Although preformed plates are suitable for repairing bones in the maxillo/craniofacial region, a moldable appliance that can be readily shaped to fill a bone defect or adapted to match the contour of the bone at a fracture site, is required for repairing all types of bones.

Second, the thermal-degradation and bulk-hydrolysis characteristics of these poly(lactic acid) (PLA) polymers make composite fabrication tedious and yield composites that can rapidly weaken in the presence of body fluids. Because of these constraints, conventional, composite-fabricating technology cannot be utilized, and the fabrication procedure that must be adopted is tedious and time-consuming.

Thus, the ultimate objective is to develop a moldable, resorbable, water-curable, orthopedic polymer from biodegradable polymers that is reinforced with CMP glass whiskers. In this project, the initial objective is to determine the feasibility of preparing isocyanate-functionalized prepolymers that can be cured by initiation with water. This improved device should be more versatile and superior to any previously developed biodegradable, moldable, orthopedic device or fracture-fixation system because of the following potential advantages, 1) customizable mechanical properties, 2) initial compliance for close apposition between the appliance and bone surfaces, 3) longer strength retention, 4) more intimate contact between fibers and matrix for better distribution of forces during periods of mechanical stress, and 5) porosity to facilitate tissue ingrowth. Ideally, the device will be an off-the-shelf material for a temporary augmentation of all types of bones and certain soft tissues. It is envisioned that it can be used after a patient has been stabilized and is free from life-threatening conditions.

Towards the initial objective, several synthetic routes were attempted to prepare isocyanate-functionalized, low-molecular-weight poly(lactic acid)s. Isocyanates were desirable because of their high reactivity towards nucleophiles such as alcohols and amines to yield urethanes and ureas, respectively. Also, their reactivity towards water to yield amines and carbon dioxide is what makes them useful in the industrial preparation of polyurea foams. As reactive materials, isocyanates can be cured quickly, and the unreacted isocyanates can be rendered harmless by water before placement into a living system. As a foamable material, the porosity of the implant can be increased to allow faster tissue ingrowth.

II. EXPERIMENTAL METHODS

A. Materials

DL-Lactide was obtained from Boehringer Ingelheim with a minimum purity of 99.0% and used without further purification. All other reagents were obtained from Aldrich Chemical Company and purified when necessary. Nuclear Magnetic Resonance spectra were obtained using a Nicolet Model NT 300NB spectrometer and tetramethylsilane as an internal standard. Gel permeation chromatography was performed on a Waters high pressure liquid chromatography, Model 501, at a flow rate of 1.5 mL/min and using two Jorgi-gel columns (500 and 10^4 Angstrom) in chloroform. Polystyrene and fatty acid esters were used as standards to calibrate the columns. Infrared spectra were obtained using a Nicolet Model MX-1.

B. Synthesis of Diol- and Triol-Terminated Prepolymers

All of the attempted synthetic schemes began with the synthesis of diol- and triol-terminated prepolymers. This step was easily accomplished by the stannous chloride-catalyzed, ring-opening polymerization of DL-lactide with a multifunctional alcohol initiator (Figure 1). Because viscous flow or moldability was a desirable feature for the ultimate isocyanate-terminated prepolymers, that property was established early in the synthetic scheme and should hold true through each step until the final product is obtained. This is based on the assumption that the molecular weight will not be increasing to any large extent to drastically change the viscosity.

Thus, to determine the appropriate ratio of initiator to monomer that will result in a viscous or moldable prepolymer, a brief investigation was undertaken by reacting the appropriate multifunctional initiator with DL-lactide. In the first step of the synthetic scheme in which ethylene glycol was reacted with lactide, it was found that a 2000 theoretical-molecular weight of the diol-terminated DL-PLA was solid at ambient temperature, whereas, a 2:1 molar ratio of lactide to ethylene glycol resulted in a reaction mixture that was a viscous liquid at ambient temperature. The theoretical-molecular weight of the oligomer from this latter reaction is 350.

When glycerol was used as the initiator instead of ethylene glycol, a 3:1 molar ratio of DL-lactide to the glycerol also resulted in a high viscosity liquid with a theoretical molecular weight of 524. However, the NMR spectrum of the reaction mixture of glycerol and DL-lactide indicated the presence of an undetermined amount of unreacted DL-lactide. This observation might indicate the nonparticipation of the secondary alcohol of glycerol in the initiation.

C. Modification of Alcohol-Terminated Prepolymers by the Succinic Anhydride Route

With the assumption that each of the three alcohol groups of the glycerol reacted with one molecule of DL-lactide, the reactions shown in Figure 2 were carried out in succession to determine if the synthetic route is practical for preparing a tri-isocyanate-terminated prepolymer. This route is slightly different from the originally proposed route shown in Figure 3 and will lead to a homolog of the originally proposed target compound. Instead of a glycine-isocyanate-terminated prepolymer, the new target is ß-alanine-isocyanate terminated. When the polymer is completely degraded, ß-alanine will be a by-product in addition to the lactic acid and the ethylene glycol (or glycerol). ß-Alanine is essential in the biosynthesis of pantothenic acid, a member of the B complex vitamins.

The new route (Figure 2) did not evolve as expected into a practical route. Initially, although there is one extra synthetic step compared to the proposed route, the new route appeared to offer two distinct advantages, 1) it precluded the use of phosgene, a toxic gas, and 2) the last step allowed for a more facile purification of the target compound because the sodium azide reagent and the sodium chloride by-product are both insoluble salts that are easily removed by filtration. The presence of unreacted acid chloride func-

tionalities were expected to be easily confirmed by the sensitive Beilstein Test for halogens.

As mentioned earlier, the reactions shown in Figure 2 were carried out in succession to determine if the synthetic route is practical for preparing a tri-isocyanate-terminated prepolymer. Thus, the viscous liquid of "triol" was reacted under bulk conditions with three equivalents (one equivalent per alcohol group) of succinic anhydride to yield a higher viscosity "triacid"-terminated prepolymer. A portion of the "triacid" prepolymer was dissolved in ethyl acetate and reacted with thionyl chloride to yield the "triacid chloride" prepolymer. The "triacid chloride" was redissolved in ethyl acetate and refluxed in the presence of sodium azide to effect a Curtius rearrangement to afford the "tri-isocyanate"-terminated prepolymer. Filtration to remove the expected sodium chloride and subsequent evaporation of the solvent yielded a product.

The infrared spectrum of the final product did not show any absorbance in the region of 2200 cm^{-1}, which would have indicated the presence of isocyanate groups. However, the Beilstein Test indicated the presence of halogens, and this led us to believe that the alcohol groups of lactic acid may not readily be reacting with the succinic anhydride. This could be due to steric hindrance because the alcohol group is secondary. As a result of their relative inertness towards the anhydride, the alcohol groups were converted to alkyl chlorides during treatment with thionyl chloride. Thus, instead of acyl chlorides, alkyl chlorides were the end-groups that were more resistant to displacement by sodium azide. Because glycerol also has a secondary alcohol group, it too could eventually be converted into an alkyl chloride, if the alcohol group did not ring-open either DL-lactide or succinic anhydride.

Because of potential problems that were becoming apparent by using glycerol as initiator, the focus shifted on the use of ethylene glycol as initiator so that only primary alcohols will initiate the ring-opening of lactide. Thus, all subsequent synthesis of the alcohol-terminated prepolymers were conducted using ethylene glycol as initiator at a molar ratio of 1:2 with DL-lactide. It was anticipated that this would eliminate some of the problems associated with secondary alcohols such as the incomplete reaction of the secondary OH's of glycerol with DL-lactide. However, secondary alcohols were still present as the end-groups of the diol prepolymer and reaction conditions must be worked out for their derivatization.

The diol-terminated prepolymer was subjected to the same first reaction of the modification scheme to determine if any derivatization was occurring at the secondary alcohols in the reaction with succinic anhydride. In the single attempt to react the diol prepolymer in bulk with two equivalents of succinic anhydride (assuming MW of diol prepolymer was 350) at 140 °C, it was found that there was an increase in viscosity. An analysis by gel permeation chromatography (GPC) revealed that the molecular weight had shifted much higher than expected, and the molecular-weight distribution had broadened. As shown in Figure 4, the peak and width of the retention time of the diol prepolymer is narrow as expected from the ring-opening reaction in which it was synthesized. Shown in Figure 5 is the chromatogram of the higher molecular weight and higher dispersity product from the bulk reaction of the diol prepolymer and succinic anhydride. From these results, it was concluded that the high reaction temper-

ature and bulk conditions led to a polycondensation in addition to the ring-opening of the cyclic anhydride.

Thus, the above reaction was repeated using ethyl acetate as solvent at reflux temperatures. After refluxing overnight, an aliquot of the reaction mixture was removed and evaporated to dryness. The residue was analyzed by GPC and a chromatogram was obtained that was found to be about identical to that of the original diol prepolymer. Infrared analysis of the same residue also revealed the presence of unreacted succinic anhydride and the absence of carboxylic acid groups. It became apparent that the reflux temperature of ethyl acetate was too low for the alcohol moieties to ring-open the succinic anhydride and yield carboxylic acid functionalities.

D. Model Studies on the Modification of the Diol Prepolymer

Because secondary alcohols were still present in the polymer as end-groups, it became necessary to work out the conditions for the subsequent reaction of the secondary alcohol groups of lactate with succinic anhydride or other derivatizing reagents. Thus, to save on the cost of the lactide monomer, the establishment of conditions for the reaction between the anhydride and the alcohol groups was begun by reacting ethylene glycol with the succinic anhydride. If successfully worked out, the conditions can be used on the diol prepolymers. In the model studies, the objective was to obtain an easily isolatable product in high yield. Using ethylene glycol as the model compound, an investigation was carried out to determine those conditions.

The justification for using ethylene glycol, which contains only primary alcohols instead of another diol which contains secondary alcohols, is as follows. If the modification of primary alcohols continues to be difficult, then it would be just as futile to attempt to derivatize the more hindered secondary alcohols. Furthermore, if the preparation of a diisocyanate compound from the model molecule is successful, it will provide a reagent that can be used as a comonomer in the telechelomerization with the diol prepolymer previously described. The reaction of the telechelomerization is shown in Figure 6.

Several reactions were investigated in an attempt to modify ethylene glycol. These reactions are shown in Figure 7. Since it was appearing that stoichiometric conditions were resulting in incomplete conversions and competing polycondensations, the effects of using excess succinic anhydride were investigated. In one example, 4 equivalents instead of the stoichiometric 2 equivalents of succinic anhydride were reacted with ethylene glycol. This reaction was done in bulk at 119 to 120 °C for 18 hours. That temperature range was selected because it was the melting point of succinic anhydride and the temperature at which the reaction mixture became a homogeneous liquid. The excess anhydride was removed by vacuum stripping without elevating the temperature. It was later determined by GPC that the anhydride was not completely removed. Furthermore, there was a broad peak in the chromatogram corresponding to a polymer [probably poly(ethylene succinate)] that overlapped with a narrow peak (Figure 8). This data led to the conclusion that the conditions for reacting the succinic anhydride with alcohols were also favorable for the competing polycondensation reactions.

Several attempts to lower the reaction temperature so that polycondensation would not compete were met with little success. In one attempt (see Figure 7), a di-alkoxide salt of ethylene glycol was prepared by reacting it with either 2 equivalents of potassium hydride or sodium metal at ambient temperature in tetrahydrofuran or bulk, respectively. Several other variations of the reaction with potassium hydroxide also were attempted with similar results. The sodium metal did not dissolve in the ethylene glycol. Because the alkoxide ion is a stronger nucleophile than an alcohol, high reaction temperatures were not necessary in the subsequent reaction with two equivalents of succinic anhydride to afford a potassium carboxylate-difunctionalized compound. Furthermore, the reason the potassium carboxylate terminals were preferred over the carboxylic acid because they are expected to have higher reactivity with thionyl chloride. Thus, one can expect higher yields.

Without purification of the dipotassium salt of ethylene glycol, it was reacted with two equivalents of succinic anhydride at the reflux temperature of the solvent (tetrahydrofuran, b.p. = 67 °C). A precipitate formed in the reaction, which, after isolation, was analyzed by mass spectroscopy and found to be the dicarboxylate salt. Without further purification of the carboxylate salt-terminated compound, thionyl chloride was added and the mixture was refluxed overnight. The reaction was then worked up by vacuum distillation.

An acid chloride-functionalized compound was isolated, but the yield was very low. The presence of acid chloride was confirmed by the Beilstein test and by testing for the presence of HCl gas, after reacting the suspected product with an alcohol, using a cotton swab that was previously soaked in ammonium hydroxide (a white ammonium chloride cloud formed). However, a NMR spectrum (Figure 9) of the compound indicated that it was more consistent with the structure of mono-(2-chloroethyl)succinyl chloride, which would result from the monosuccinylation of the ethylene glycol followed by the conversion of alcohol and the carboxylic acid to alkyl halide and acid halide (Figure 10), respectively.

In addition to the acid chloride, succinic anhydride was also isolated as shown previously in the NMR spectrum. Thus, the reaction was not going to completion. Attempts to optimize this reaction to produce enough acid chloride for later reactions with sodium azide did not provide high conversion and gave low yields. One attempt to increase the yield by eliminating the solvent resulted only in a blackened reaction mixture (decomposition) because the melting temperature of succinic anhydride (119 °C) was too high for the reaction. Thus, the use of succinic anhydride as a modification reagent was abandoned.

E. Modification of Ethylene Glycol by the α-Haloacetyl Halide Route

The next efforts focused on investigating the utility of more reactive reagents for modifying alcohol groups. Again, using ethylene glycol as the model compound, alternate routes were attempted as outlined in Figure 11. If the scheme is adapted for modifying the diol-terminated-PLA prepolymer, the originally proposed target compound (Figure 3) could be afforded. The routes also have one more step than in the originally proposed route, but the advan-

tages of safety and potential ease of purification of the reaction products outweighs this.

The first step in the routes was attempted using ethylene glycol as the model starting material to represent the alcohol-terminated prepolymer. The reaction was found to be quite facile, as expected, because of the good reactivity between an alcohol and an α-haloacetyl chloride. The product was easily purified by vacuum distillation. Ethylene bis(2-bromoacetate) and bis(2-chloroacetate) were prepared and were reacted separately by heating in the presence of potassium cyanate (KOCN). The reactions were worked up by distillation to isolate the expected products. Because the IR spectra of the products did not have the characteristic absorbance of the isocyanate functionality, it was concluded that both of the derivatives, when reacted with KOCN, resulted in the recovery of the starting material.

Precedence for the displacement of halides with cyanates has been reported (Holm and Wentrup, 1966), but the alkyl iodides are the best examples for preparing alkyl isocyanates. With the primary halide, n-propyl iodide as an example, yields of 75% have been reported. Unfortunately, 2-iodoacetyl chloride is not readily available to prepare the desired derivative for reaction with KOCN.

However, the two previously synthesized 2-haloacetyl derivatives can still be converted to 2-iodoacetyl derivatives by halogen exchange. This is an equilibrium process that takes advantage of the fact that KI or NaI salts are soluble in acetone, and the resulting KCl or NaCl salts are insoluble. When an alkyl bromide or chloride is treated with a solution of KI or NaI in acetone, the equilibrium is shifted by the precipitation of the insoluble KCl and NaCl salts. Thus, halogen exchange can be used to prepare alkyl iodides. The product from the halogen exchange should be easy to purify by vacuum distillation.

The synthesis of the 2-iodoacetyl derivative for the subsequent reaction with potassium cyanate was attempted in the manner described above. Unfortunately, the isolated product from the vacuum distillation, which was suspected to be the desired compound, was found to be unstable as evidenced by darkening of the compound upon exposure to light.

Therefore, the utility of NaI as a catalyst in the second step of the scheme was investigated (see Figure 11). It was rationalized that if the 2-iodoacetyl derivative could be generated in situ, it would be available to react immediately with the cyanate ion without having to isolate it. Thus, the ethylene bis(2-chloroacetate) was reacted with sodium cyanate (NaOCN) in the presence of a catalytic amount of NaI by refluxing in acetone. The reaction was worked up by distillation in an attempt to isolate the expected diisocyanate product. Unfortunately, another light-sensitive compound was isolated, which gave a positive Beilstein Test for halogens.

Thus, another procedure was attempted to transform the halide functionalities into isocyanates. At this point in the project, there was a sense of urgency to isolate compounds having isocyanate functionalities so there would be spectral benchmarks for later comparisons. Thus, a procedure was adapted (Holm and Wentrup, 1966) whereby the bromides of ethylene bis(2-bromoacetate) were displaced with isocynates by treating them with silver cyanate. Because

of the high affinity of silver for halogens, the bromides were readily displaced by the isocyanate. The isocyanate functionality was confirmed by its absorbance at 2260 cm^{-1} in its IR spectrum (Figure 12). The procedure was not found to be a practical approach, thus, was not adapted in the large-scale preparation of diisocyanate-containing prepolymer. The procedure is impractical because the yield was low and the reagent is expensive.

F. Modification of Diol Compounds by the Diacid Chloride Route

Having encountered the difficulties in elaborating an isocyanate functionality from carboxylic acids and from alkyl halides, another approach (Figure 13) was considered in which the diol prepolymer was reacted with excess diacid chloride to afford a diacid chloride-terminated prepolymer that could be subsequently converted into a diisocyanate prepolymer. Because of the tendency of a polycondensation reaction to occur when difunctional compounds are reacted, such as in the reaction of the ethylene glycol and succinic anhydride, the next approach was advanced whereby any competing polycondensation would not be a detriment. This was accomplished by treating the diol with an excess of the diacid chloride so that the terminal groups would be acid chlorides.

Although polycondensation can still be expected, the use of succinyl chloride instead of succinic anhydride offers two advantages. First, it is liquid and it is more volatile than succinic anhydride, and second, it is also more reactive towards alcohols. Thus, unlike succinic anhydride, high temperatures will not be necessary to remove the excess succinyl chloride and transesterifications, and polycondensations can be avoided or minimized. Thus, purification is achieved by removal of volatiles at low temperatures. However, it is important to use pure starting materials so that nonvolatile impurities will not carry over into the next synthetic step and ultimately remain within the product. Thus, all reagents were purified by distillation prior to use.

Using ethylene glycol as a model compound, it was reacted with an excess of succinyl chloride. As expected, oligomerization did occur because attempted isolation of a major product by vacuum distillation did not yield a major product. However, qualitative tests confirmed the necessary functionalities from the expected oligomeric products. For example, the Beilstein test for halogens was positive, and in the IR spectrum (Figure 14) both the absorbance peaks for the acid chloride (1787 cm^{-1}) and the ester (1735 cm^{-1}) were observed. Interestingly, a peak at 1865 cm-1 was also detected, which indicated the presence of succinic anhydride. This was also confirmed in the NMR spectrum. The formation of succinic anhydride was probably due to the contamination by moisture, which is difficult to exclude because of the hygroscopic nature of ethylene glycol. Thus, partial hydrolysis of the succinyl chloride was followed by the cyclization to yield succinic anhydride.

The model reaction was then tried on the diol prepolymer (Figure 13). The reaction was done in bulk at ambient temperature under nitrogen with mechanical stirring. The diol prepolymer was added dropwise with a syringe into the freshly distilled succinyl chloride. The addition was performed in such a manner that the evolution of HCl gas was not too vigorous. Because the reaction was exothermic, the temperature of the reaction mixture rose to 35 °C. After completion of the addition, the reaction mixture became cloudy with a

slight yellow color. After about 5 hours from the completion of the addition, the reaction temperature returned to room temperature and the cloudiness disappeared, but a slight yellow color remained. Also, the viscosity became too great for the mechanical stirrer to handle, and the stirring had to be discontinued. However, the viscosity increase was not substantial enough to cause the reaction mixture to solidify. The increase in viscosity is attributed to a probable increase in molecular weight as a result of the accompanying polycondensation. The reaction was then worked up by applying vacuum for 24 hours to remove any unreacted succinyl chloride and hydrogen chloride.

Elemental analyses of the diacid chloride showed 43.86% carbon and 4.76% hydrogen, which is slightly lower than the theoretical values of 44.99% and 4.81%, respectively. The discrepancy calculates to a 10.3 mole % (or 2.73 wt %) contamination by the succinyl chloride, assuming that it is the only contaminant present. Also, the stannous chloride catalyst was still present, but the elemental analysis of the diol precursor found 47.91% carbon and 6.41% hydrogen, which are in agreement with the theoretical values of 48.00% and 6.33%, respectively. Thus, the catalyst was not a significant contaminant as evidenced by the 26.7 ppm concentration that was found in the analysis of the diol precursor by atomic absorption spectroscopy. The diacid chloride was also analyzed by atomic absorption, and the tin concentration was found to be 7.1 ppm. Another contaminant that may have been present was hydrogen chloride, but it was unlikely that the large molar content necessary to cause the discrepancy noted was present. In all likelihood, both the diacid chloride and the hydrogen chloride were present in some undetermined amounts.

A new procedure was then adapted to transform the acid chlorides into isocyanates. The procedure was adapted from a report indicating that a bulk reaction between an acid chloride and the azidotrimethylsilane at stoichiometric conditions (see Figure 13) can afford good yields (Washburne and Peterson, 1971). A bulk reaction is highly desirable because it precludes the use of solvents and eliminates another potential contaminant. Azidotrimethylsilane is preferred over sodium azide to effect a Curtius rearrangement because the by-products, chlorotrimethylsilane and nitrogen, are volatiles, which should facilitate purification. This was in contrast to the filtration of reaction solutions to remove sodium chloride and the subsequent evaporation of the solvent if sodium azide was used. Azidotrimethylsilane is commercially available and is prepared by the reaction of chlorotrimethylsilane with sodium azide. Furthermore, if any of the reagent does not react, it is also volatile (b.p. = 53 °C/175 mm Hg) and should be removed easily from the product by application of vacuum.

In a reaction of the azidotrimethylsilane with the supposed diacid chloride prepolymer, an excess of the reagent was used in an attempt to effect a higher yield. The azidotrimethylsilane was added dropwise to the prepolymer under nitrogen at 50 °C. An immediate reaction was noted upon addition of the first drops. When a sufficient amount of the reagent had been added to sufficiently lower the viscosity, the mechanical stirring was started, and the addition was continued. The reaction was exothermic and was accompanied by a rapid evolution of nitrogen. In an attempt to control the reaction, the addition of the azidotrimethylsilane was periodically interrupted. However, before the addition could be completed, the reaction flask shattered.

Because there were not any unusual hazards reported in the procedure that was being adapted, a survey of the literature was conducted to determine if the use of azidotrimethylsilane had been hazardous previously. There were no reports that the compound by itself was explosive. However, it was reported (West and Ziegler, 1984) that in a synthesis of the reagent when aluminum chloride was used as catalyst, a violent detonation occurred. The authors attributed the detonation to the formation of traces of aluminum azides. Analogously, in the case of the reaction with the diacid chloride prepolymer, the presence of the stannous chloride may have led to the formation of explosive, metallic azides.

Thus, the synthetic scheme was carried out again from the beginning, starting with the ethylene glycol and DL-lactide. In this case, no catalyst was used in the first step. The appearance of the product did not seem to differ from the one that was synthesized in the presence of the catalyst. Also, the NMR spectrum was very similar to the catalytically synthesized polymer.

When the last reaction of the synthetic scheme was again tried, no explosion was encountered. However, the final product was solid and had no moldability. It was dissolved from the reaction flask in chloroform, and a film was cast from the solution. After drying, the film did not become brittle, but was flexible and weak. It was analyzed by IR spectroscopy, but the analysis did not indicate any presence of isocyanates. However, there were very broad peaks between 1825 and 1650 cm^{-1} and between 3450 and 3325 cm^{-1}, which correspond respectively to carbonyl and amide N-H absorptions. The amide N-H absorptions would support the presence of either the urea or urethane linkage. Because the film casting was not performed under the exclusion of moisture, it possibly led to the decomposition of some of the isocyanates into amines, which were then available to react with the free isocyanates to form a urea linkage. This is exactly the mechanism that had been envisioned for the curing of the prepolymer.

III. CONCLUSIONS AND RECOMMENDATIONS

The goal of this project was to demonstrate the feasibility of synthesizing isocyanate-functionalized prepolymers for further evaluation as a matrix polymer in the fabrication of totally resorbable composites. The prepolymer was designed to be a liquid or moldable solid and was based on the same types of monomers that were used previously to fabricate the completely resorbable, internal, fracture-fixation devices. Successful synthesis of a biocompatible, moldable, resorbable, and water-curable polymer as matrix for CMP glass whiskers will ultimately lead to the elimination of the deficiencies in the present device.

The motivation for the development of such a polymer arose from two deficiencies in the previously developed devices. One deficiency is the difficulty of reshaping the fixation appliance to closely match the contour of the mandible at the time of surgery. The second deficiency is the strength-loss at the fiber-matrix interface that had been attributed to the capillary action of water along the interface from the exposed fiber ends. This second deficiency

is inherent to the lamination technique that was used to fabricate the fixation devices.

There were basically three modification schemes that were attempted that differed in the compound that was reacted with a di- or trifunctional alcohol. In two of the schemes, the ultimate end-groups were to be similar. These were the attempted modifications using succinic anhydride and succinyl chloride, which would have ultimately yielded polymers that will eventually degrade to give ß-alanine as one of the by-products. In the third scheme, an α-haloacetyl halide was used as the modification reagent. One of the degradation by-products from polymers derived by this scheme would be glycine.

In this project, the synthesis of the isocyanate-functionalized prepolymers proved to be elusive. It was concluded that there were primarily two problems, which were interrelated, that were encountered in modifying the diol or triol prepolymers. These problems should be considered in any future attempts of modifying polymers for use in biomedical applications. The problems were basically concerned with, 1) the removal of impurities, and 2) the yields of the reactions. If the impurities are not adequately removed before and/or after each and every reaction, they may affect the yields of the subsequent reactions. If the yield of a reaction is low, the presence of unreacted reagents may affect the subsequent steps. Thus, it is highly desirable to employ reactions that are known to give high conversions (yields) and high selectivity using reagents that can be removed easily from the reaction mixture or are inert to the reagents in the subsequent synthetic scheme. If the reagents are inert to the subsequent reactions and are left as contaminants, it will be required that they be biocompatible.

Thus, future work should include investigations of synthetic schemes with the aforementioned considerations. For example, cross-linking agents can be developed from naturally occurring compounds, such as some amino acids. These cross-linking agents should be designed to be large enough to have slow diffusions characteristics and be reactive towards water and nucleophiles, such as the end-groups of the prepolymer. As such, if any of it remains after cross-linking the prepolymer, it will be slow to diffuse out of the implant and will be rendered harmless when decomposed into the original amino acid by the infiltrating water.

Another objective in any future work should be the development of cross-linking agents that will use directly the alcohol-terminated prepolymers of lactide in the cross-linking. As such, only one step will be necessary to prepare the prepolymer by the ring-opening polymerization of lactide using a polyol as an initiator. For example, it has been demonstrated that star polymers can be synthesized when natural polyols, such as inositol, are used as initiators in the polymerization of lactide (Bruin et al., 1988).

VII. REFERENCES

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APPENDIX

(Figures 1 through 14)

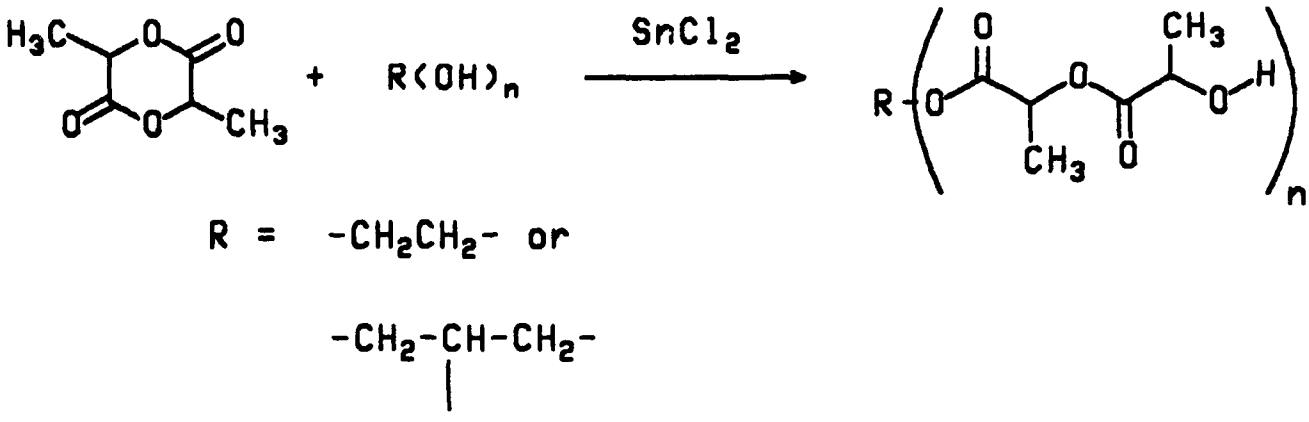
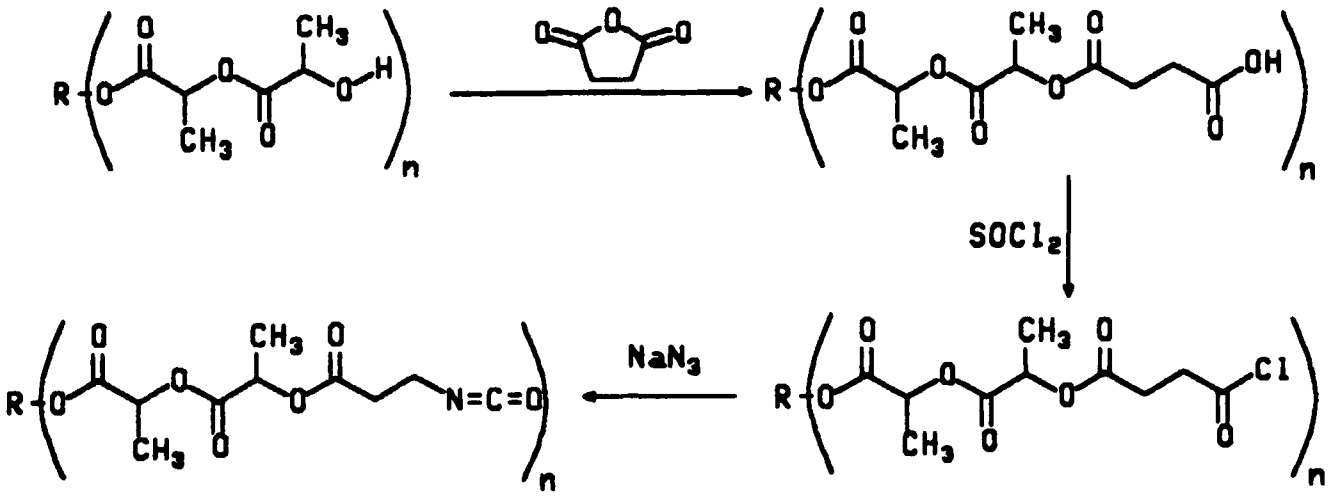


Figure 1. Preparation of alcohol-terminated prepolymers.



R = $-CH_2CH_2-$ or

$-CH_2-CH(CH_3)-CH_2-$

Figure 2. Modification of alcohol-terminated prepolymer by the succinic anhydride route.

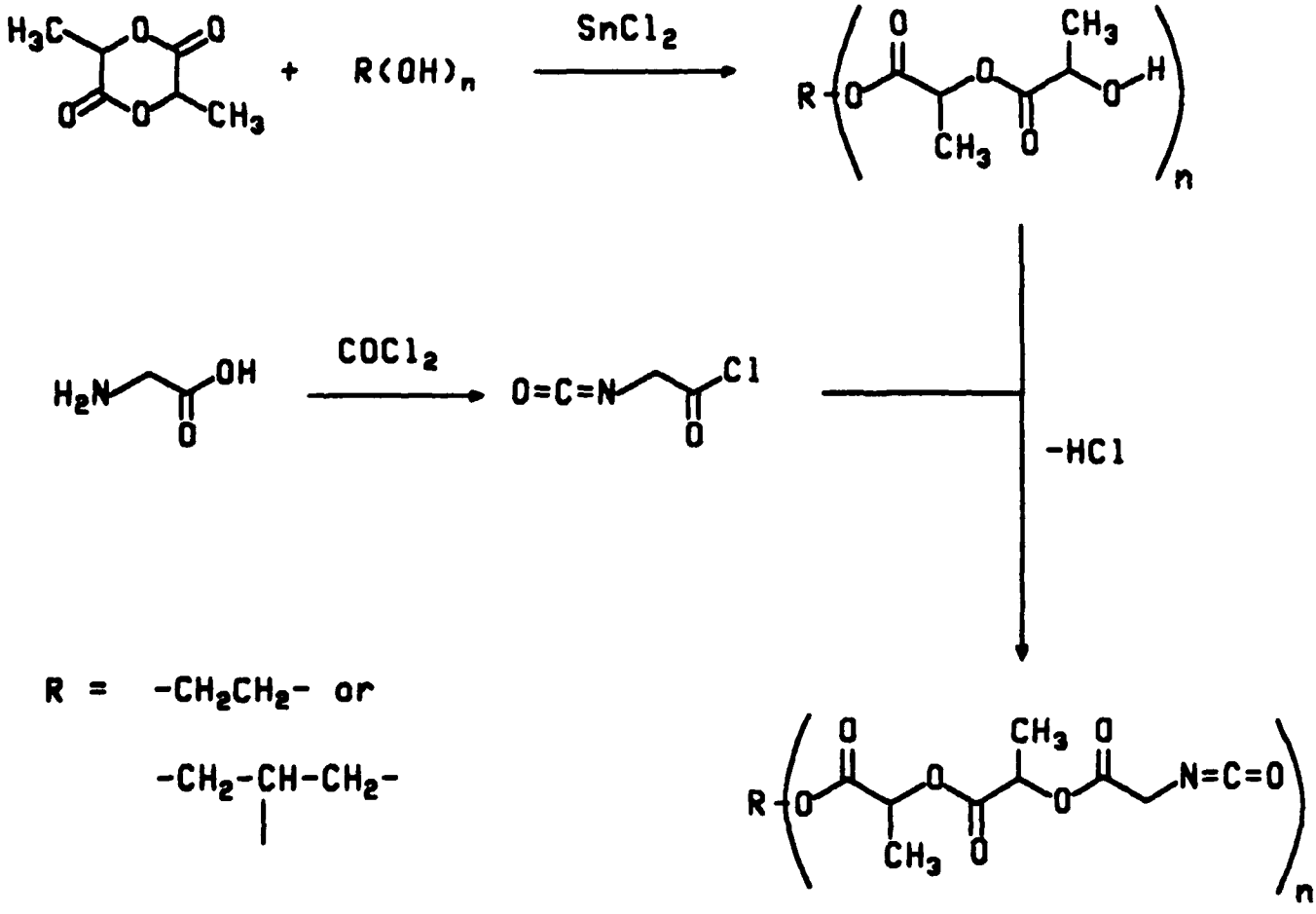


Figure 3. Originally proposed route to isocyanate-terminated prepolymer.

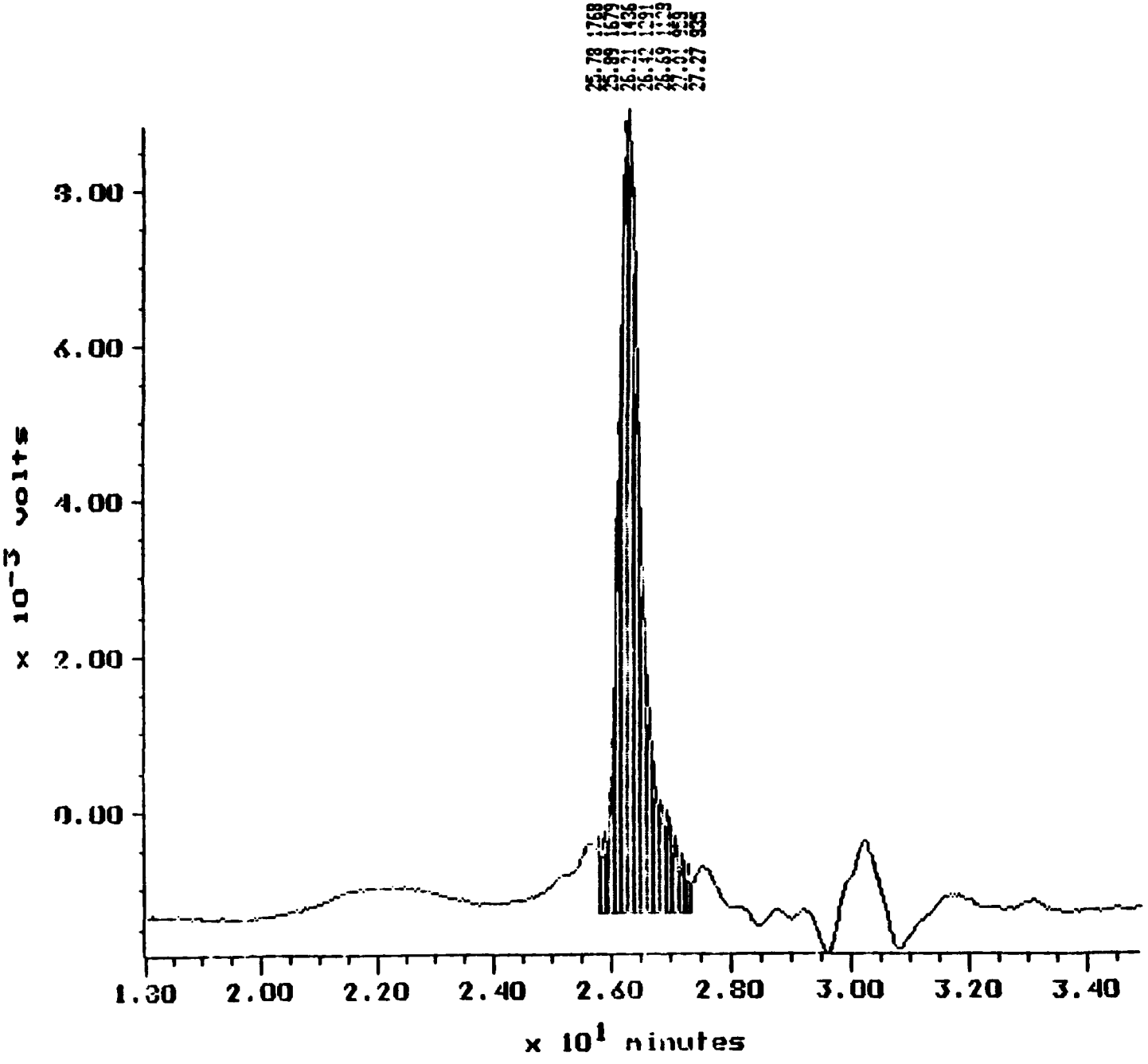


Figure 4. Gel permeation chromatogram of diol prepolymer prepared by the stannous chloride catalyzed reaction of ethylene glycol with DL-lactide.

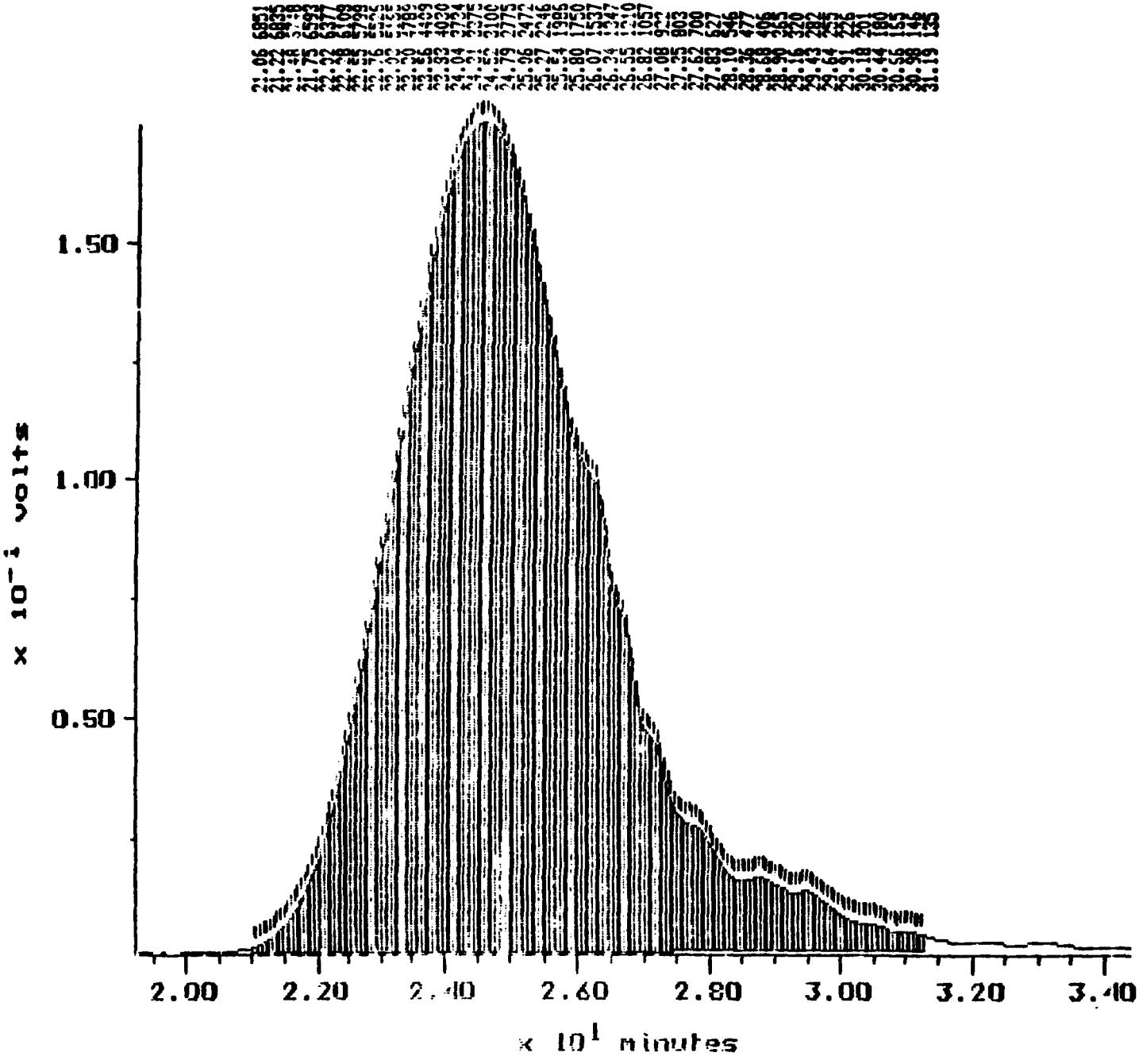


Figure 5. Gel permeation chromatogram of the product from the reaction of diol prepolymer with succinic anhydride.

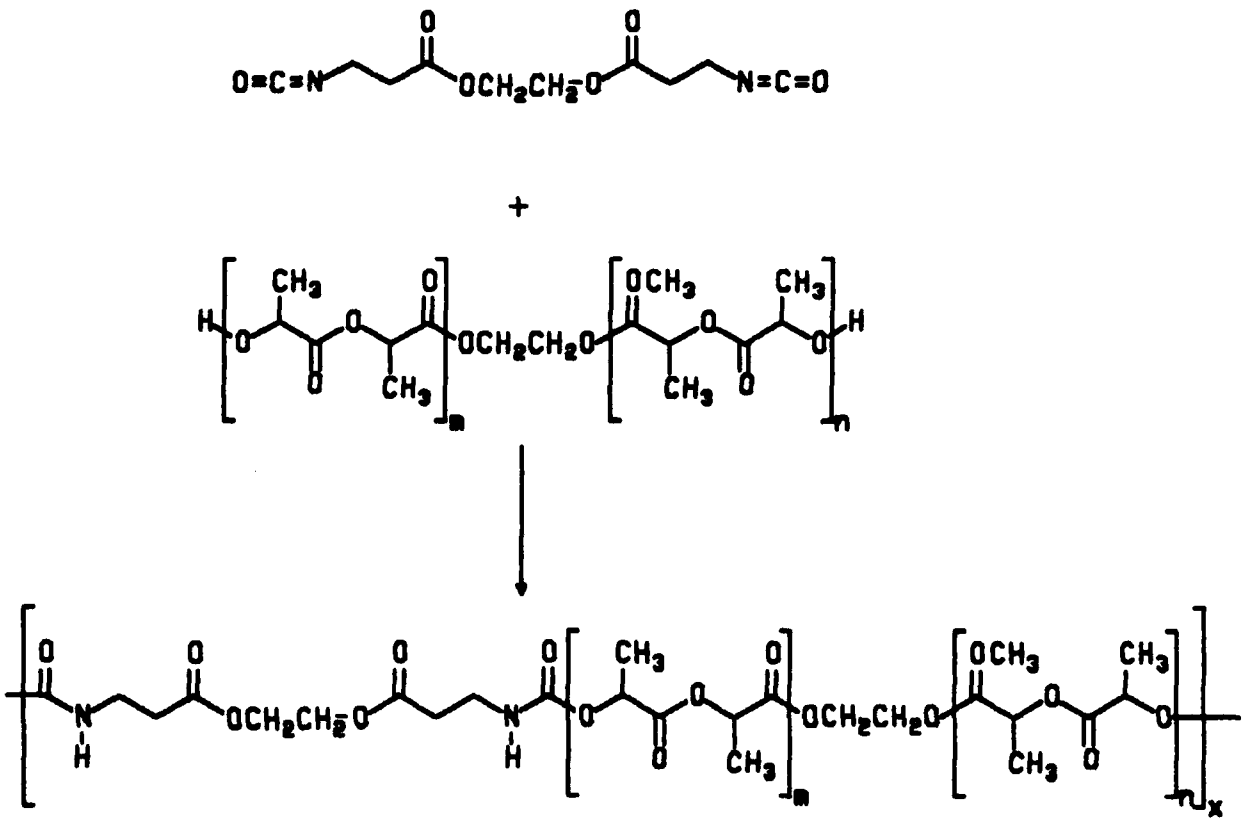


Figure 6. Reaction of diol prepolymer with diisocyanate-model compound.

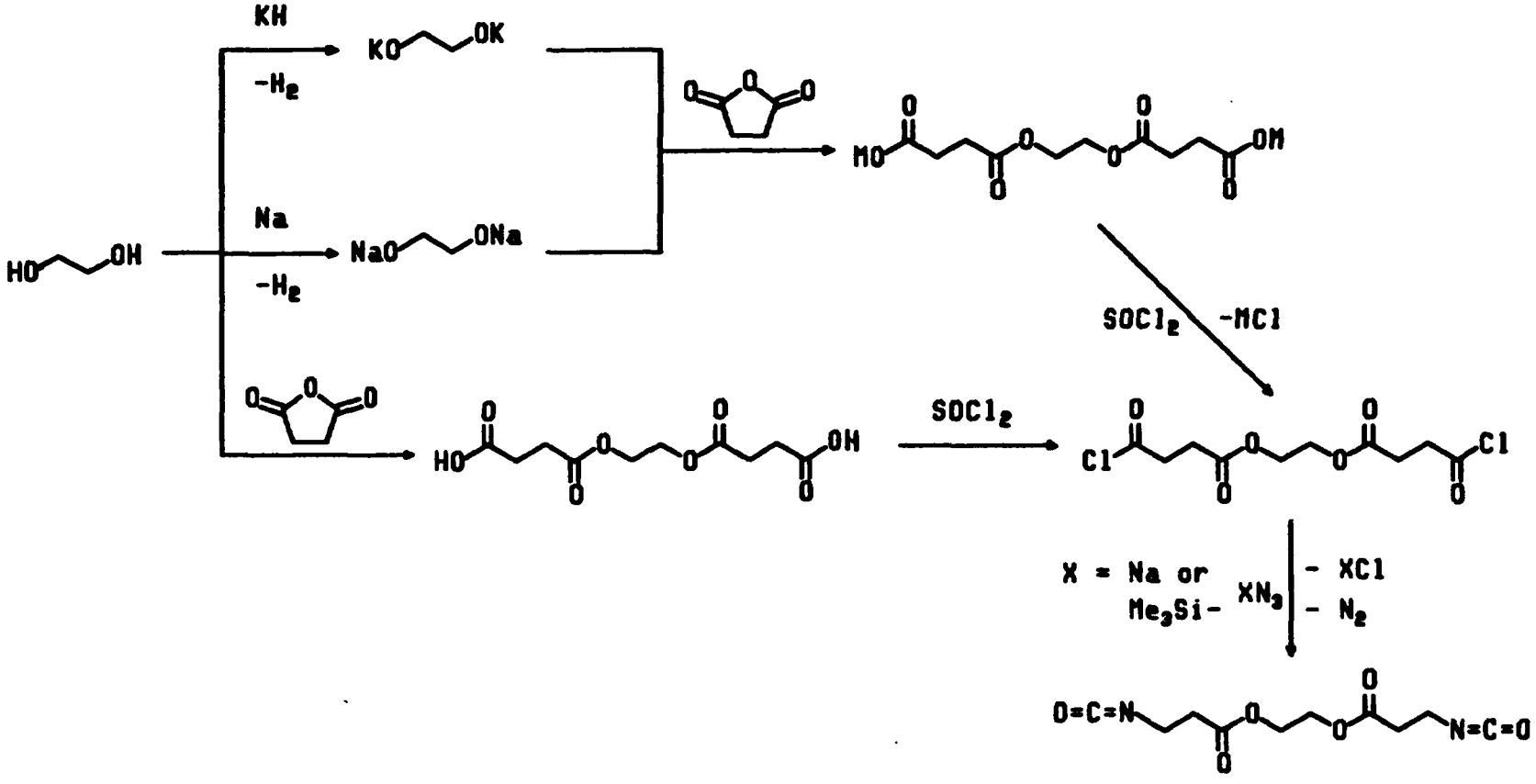


Figure 7. Synthetic routes to modification of ethylene glycol.

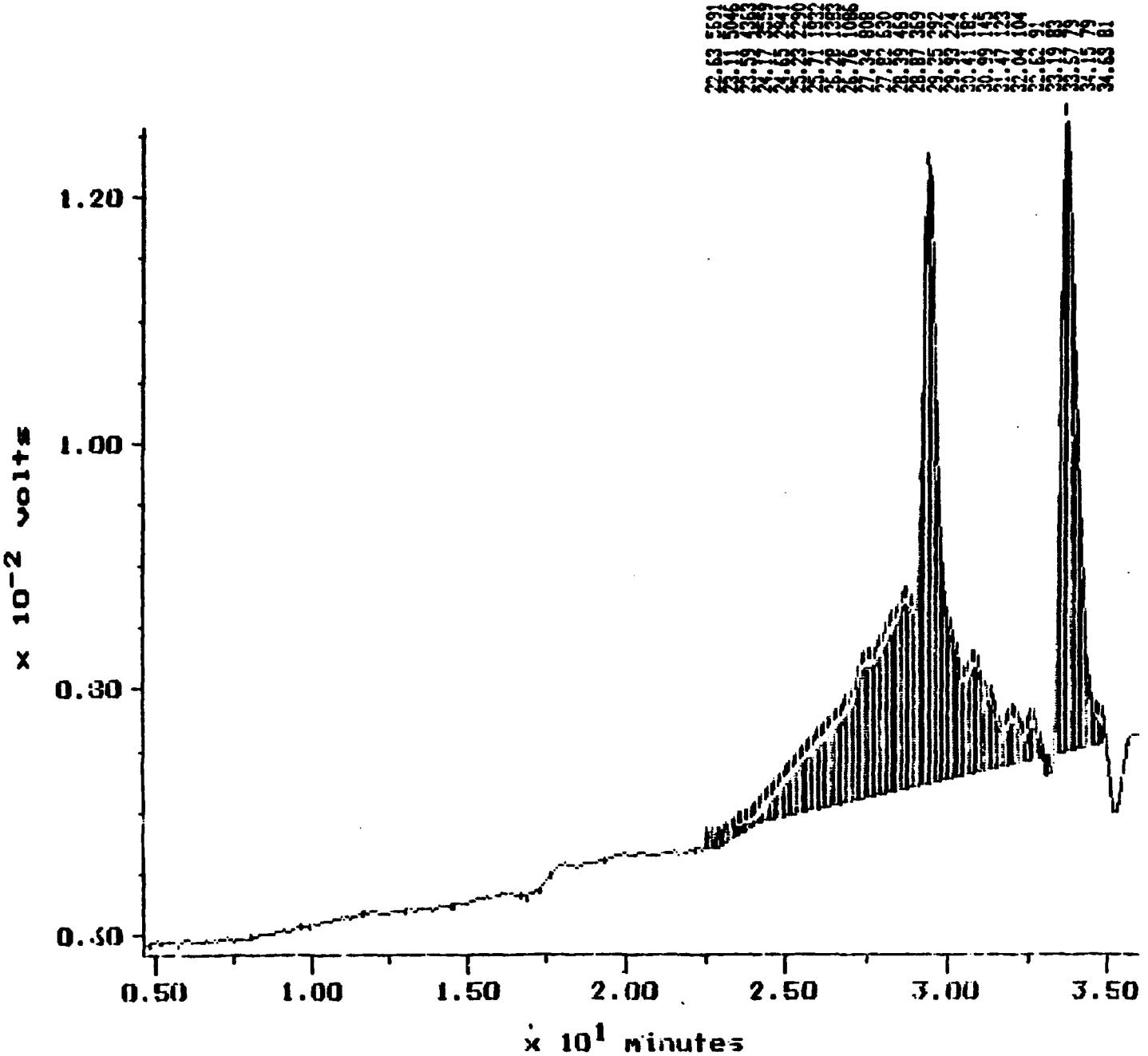


Figure 8. Gel permeation chromatogram of the product from the reaction of ethylene glycol with succinic anhydride.

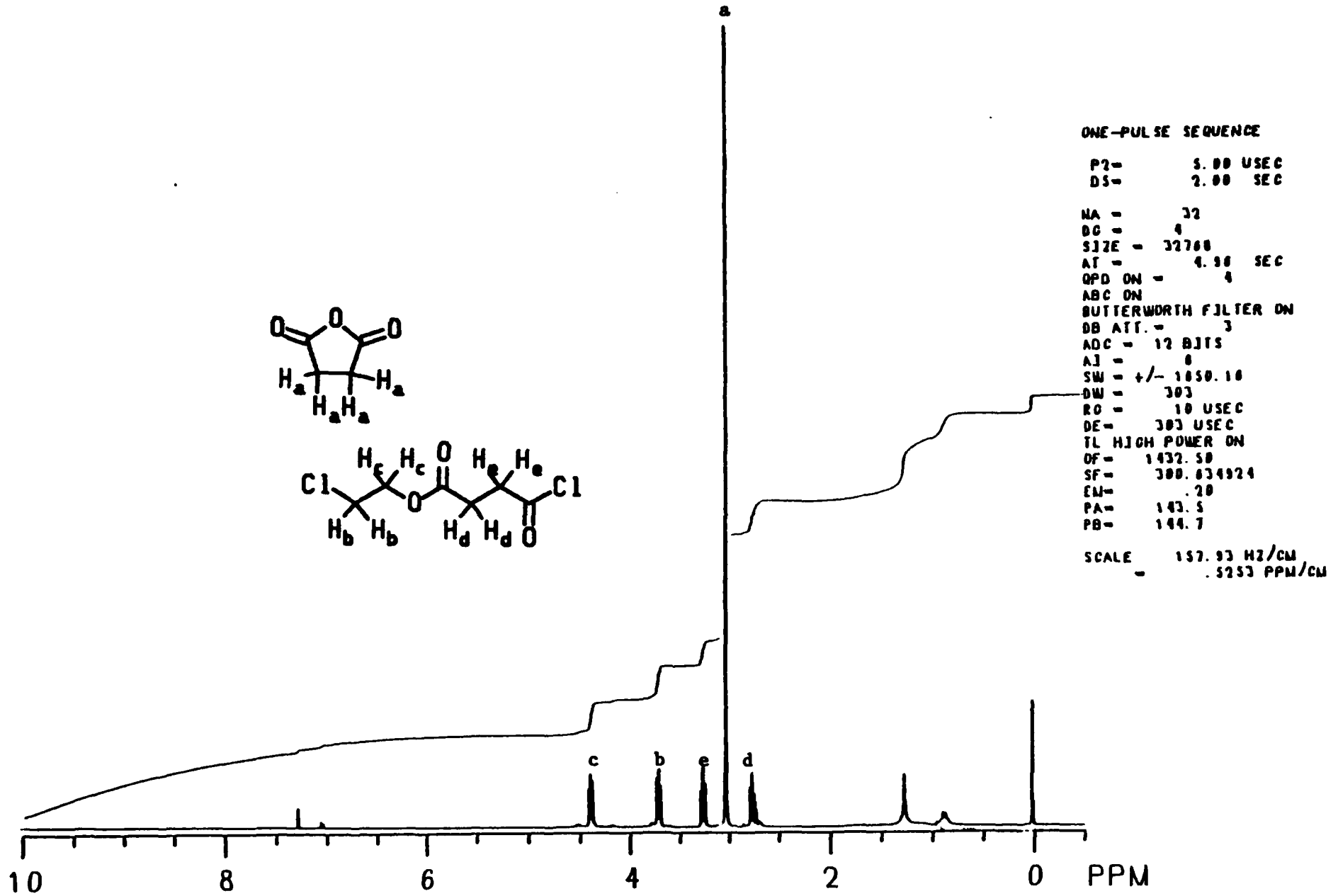


Figure 9. ^{1}H-NMR spectrum of the end-product from the reaction of ethylene glycol with succinic anhydride and thionyl chloride as shown in Figure 10.

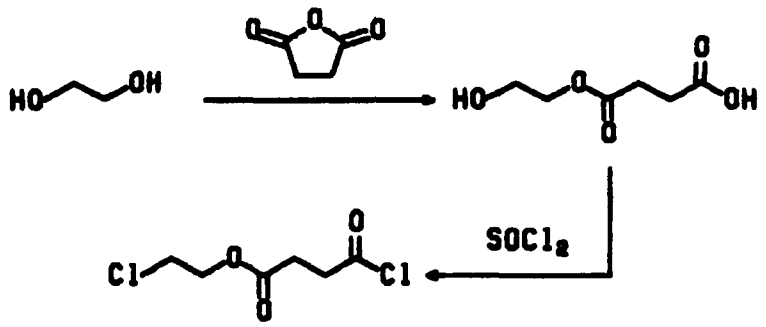


Figure 10. Potential side products from modifications of ethylene glycol.

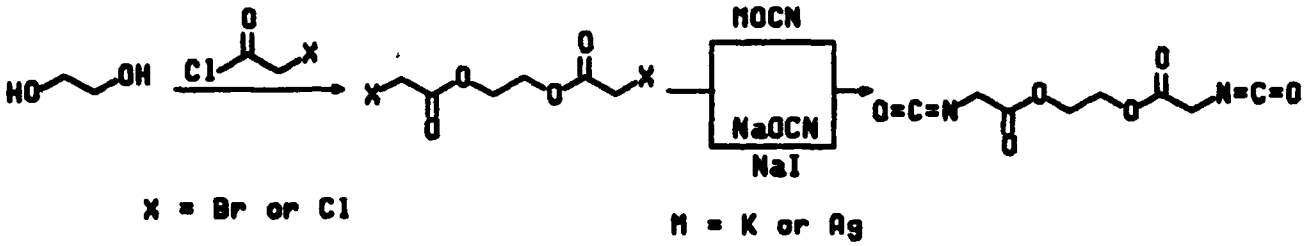


Figure 11. Modification of ethylene glycol by the α-haloacetyl chloride route.

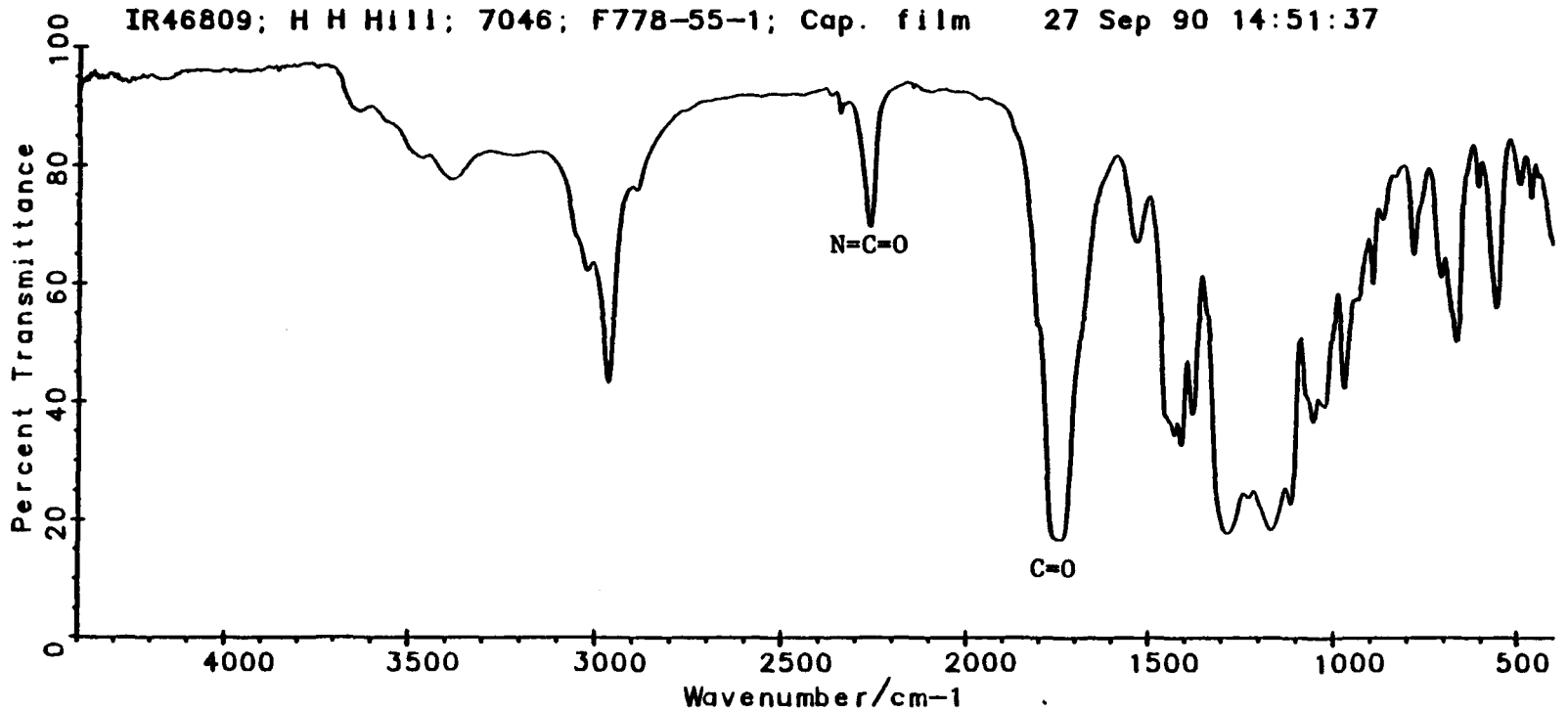


Figure 12. Infrared spectrum of the product from the reaction of ethylene bis(2-bromoacetate) and silver cyanate.

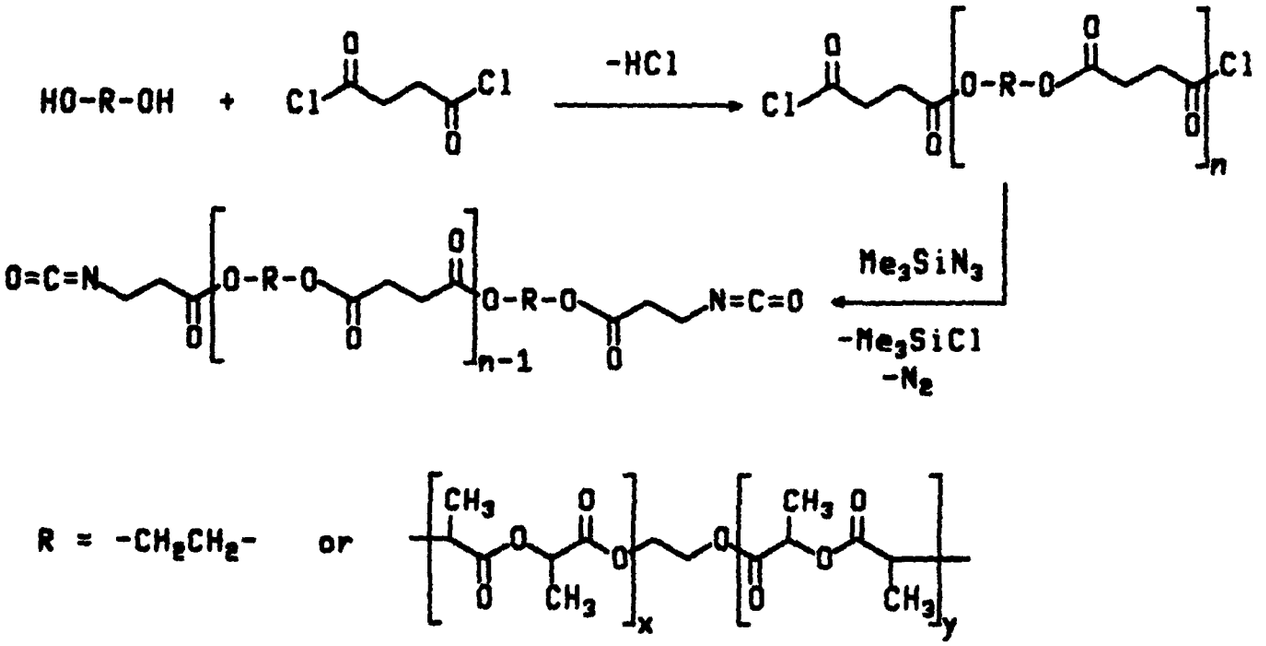


Figure 13. Modification of diols by reaction with excess diacid chloride.

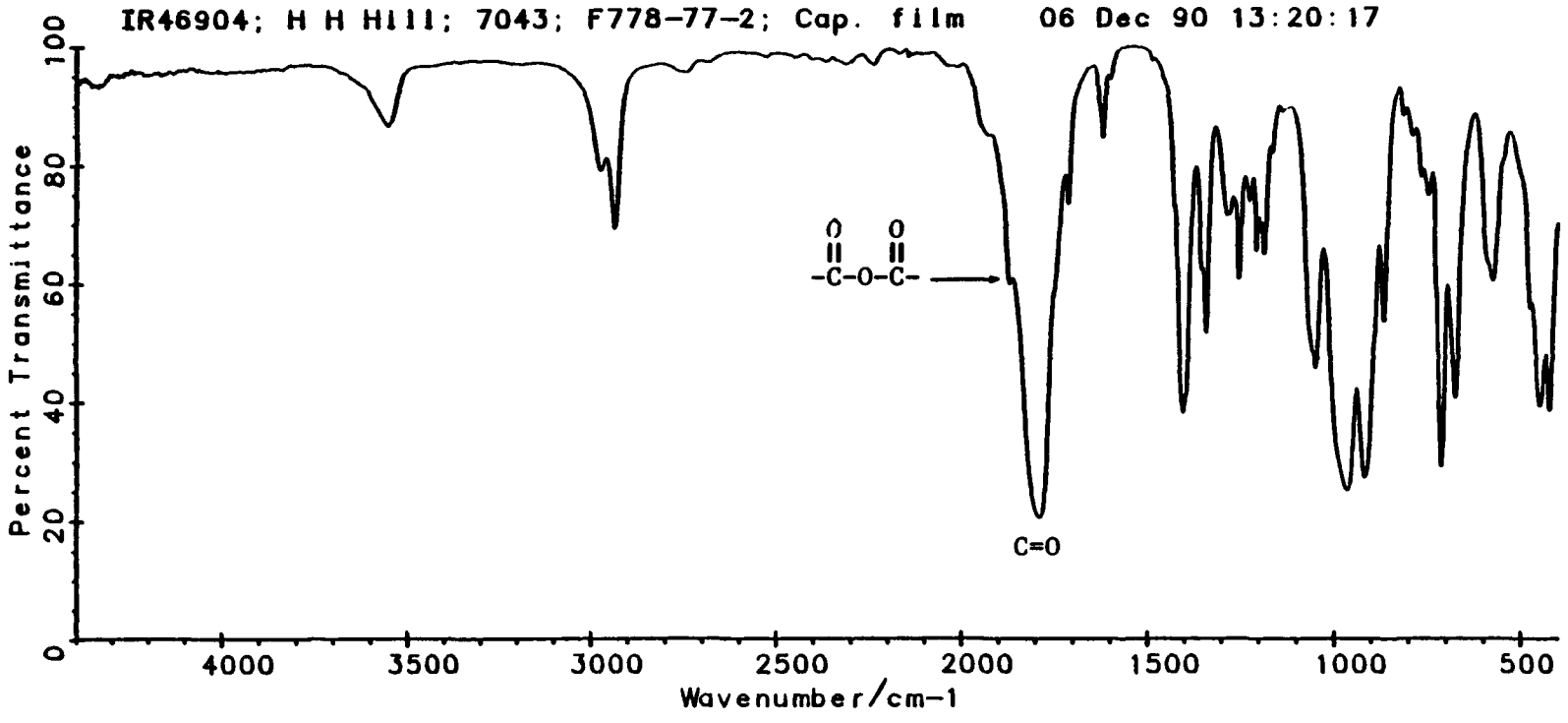


Figure 14. Infrared spectrum of the product from the reaction of ethylene glycol and succinyl chloride.